UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,498	06/07/2006	Siegfried Ansorge	013183.00055	1382

26712 7590 12/23/2008

HODGSON RUSS LLP
THE GUARANTY BUILDING
140 PEARL STREET
SUITE 100
BUFFALO, NY 14202-4040

EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
12/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,498	ANSORGE ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-24* is/are pending in the application.

4a) Of the above claim(s) *1-4,6-12,15-21 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5, 13, 22, 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/9/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment after Non-Final rejection filed on September 19, 2008 is acknowledged. Claim 14 has been cancelled and new claims 18-24 have been added. Applicant elected Group II and species (Lys[Z(NO2)thiazolidide) as DP IV inhibitor, actinonin as the SPN inhibitor, benign fibrotic and sclerotic diseases as the species of diseases, oral as the systemic application, and creams as the topical application in the reply filed on January 17, 2008. Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election was treated as an election without traverse. The Restriction requirement was deemed proper and made FINAL in the previous office action. Claims 1-4, 6-12 and 15-17 remain withdrawn from further consideration, as being drawn to nonelected inventions. New claims 18-21 and 23 are withdrawn from further consideration, as being drawn to nonelected species. Claims 5, 13, 22 and 24 are examined on the merits in this office action.

Withdrawn Objections and Rejections

1. The objection to the specification is hereby withdrawn in view of Applicant's amendment of title to "COMBINATIONS of ENZYMES INHIBITORS and the USE THEREOF".

2. The objection to the specification having inconsistency in the spelling of "Actinonin" and spelling error of "Figure" is hereby withdrawn in view of Applicant's amendment.

3. Rejection of claims 5 and 14 under 35 U.S.C. 112, second paragraph, are hereby withdrawn in view of Applicant's amendment to the claims.

4. Rejection of claims 5 and 13-14 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is hereby withdrawn in view of Applicant's amendment to the claims.

Maintained Rejection

35 U.S.C. 112, 1st

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 5 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the

genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a method for therapy in an individual in need of treatment for benign fibrotic and sclerotic disease comprising administering to the individual in need of the treatment inhibitors of dipeptidyl peptidase IV (DPIV) as well as of inhibitors of enzymes having an equal substrate specificity (DPIV-analogous enzyme activity) or/and of inhibitors of alanyl aminopeptidase (aminopeptidase N, APN) as well as of inhibitors of enzymes having an equal substrate specificity (APN-analogous enzyme activity). The generic statements inhibitors of enzymes having an equal substrate specificity (DP IV analogous enzyme activity), inhibitors of enzymes having an equal substrate specificity (APN analogous enzyme activity) do not provide ample written description for the compounds since the claims do not describe a single structural feature. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention.

As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claims 5 and 13 are broad generics with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to any class

of peptide or a peptide-like molecule that can form peptide bonds and make up the class of DP IV analogs, APN analogs, and other compounds that have the same enzyme activity. It must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives. The specification is void of organic molecules that functions as a peptide-like molecule that qualify for the functional characteristics claimed as a peptide or a peptide-like molecule or other peptidic molecules, and other synthetic peptide or peptide-like molecule that can function as proteases.

The specification is limited to the Lys[Z(NO_2)]thiazolidide (I49) and phosphonic acid diaryl ester (I63), dipeptide boronic acids and their salts, Xaa-Xaa-(Trp)-Pro-(Xaa)n peptides and amino acid-(Xaa) amides for DP IV inhibitors and actinonin, bestatin, probestin, phebestin, RB3014 or leuhistin for APN inhibitor (see paragraphs [0012]-[0013]). The specification discloses that the preferred effectors for DP IV are for example Xaa-Pro dipeptides, corresponding derivatives and their salts (see paragraph [0012]). The specification discloses that the preferred inhibitors of APN are bestatin

(Ubenimex), actinonin, probestine, phebestine, RB3014 or leuhistine (see paragraph [0013]). The working example describe the dose-dependent inhibition of DNA synthesis of I49 (DP IV inhibitor) and actinonin (APN inhibitor) on human fibroblast cells in vitro (see Example 1). The specification does not describe any other inhibitors of DP IV, such as dipeptide derivatives and Xaa-Xaa-(Trp)-Pro-(Xaa)n derivatives that would encompass the derivatives and variants of Xaa-Pro dipeptide derivatives. Descriptions I63, Xaa-Pro and Lys[Z(NO_2)]thiazolidide (I49) for DP IV inhibitors and bestatin (Ubenimex), actinonin, probestine, phebestine, RB3014 or leuhistine for APN inhibitors are not sufficient to encompass numerous other proteins and derivatives that belong to the same genus. For example, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus. There are 20 naturally occurring amino acids that can be used as Xaa. Additionally, there are non-naturally occurring amino acids, such as D-amino acids, and amino acid mimetics or peptidomimetics, and other modified amino acids that can be substituted for Xaa to increase the number of possibilities. Furthermore, Xaa-Xaa-(Trp)-Pro-(Xaa)n peptides and their corresponding derivatives and salts would have vast number of possibilities, since n can be 0 to 10. Since there are 20 naturally occurring, and D-isomers and amino acids mimetics or peptide mimetics and other modified amino acids, the peptides and derivatives are innumerable. There would be at least 20 different possibilities for the first Xaa, and at least 20 different possibilities for the 2nd Xaa and at least 20 amino acid possibilities for the 3rd Xaa. Since the 3rd Xaa can be 0 to 10 amino acids, this further increase the numbers of possibilities for this peptide alone. Furthermore, side chain

protected derivatives could be anything, even a side chain that has been modified with an amino acid or an alkyl group. Therefore, the numbers of possibilities are innumerable. Additionally, α-aminophosphinic acid derivatives would further increase the APN inhibitor derivative possibilities since the derivatives can be anything, and the limits (types of modification, variance and homologous) are not provided in the specification. Additionally, many compounds can function as inhibitors of DPIV and APN enzymes. Here, claims recite some functional characteristics, however, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Therefore, there is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Response to Applicant's Arguments

7. Applicant argues that "the instant application does not claim new APN or DP IV inhibitors. Rather, Applicants have discovered a new use for known inhibitors of APN and CP IV, for treating dermatological diseases." Applicant argues that "there are many species of APN inhibitor known in the art such that the recited genus is readily recognizable to one skilled in the art."

8. Applicant's arguments have been fully considered but have not been found persuasive. The claims recite inhibitors of enzymes having an equal substrate specificity (DPIV-analogous enzyme activity) and inhibitors of enzymes having an equal substrate specificity (APN-analogous enzyme activity). This implies any compound having equal substrate specificity. Any and all compounds having the activity and functionality would meet the limitation of the DPIV-analogous enzyme activity and APN-analogous enzyme activity. These compounds include more than the known DPIV and APN inhibitors. The instant disclosure provides no guidance with respect to the "inhibitors of enzymes having DP IV-analogous activity" and how one of skill in the art would find such enzymes and inhibitors thereof. Furthermore, instant disclosure provides no guidance with respect to "inhibitors of enzymes having APN-analogous activity" and how one of skill in the art would find such enzymes and inhibitors thereof. Therefore, Applicant was not in possession of all of inhibitors of DPIV and APN enzymes at the time the application was filed.

35 U.S.C. 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 5, 13, 22 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Ansorge (WO 02/053170 (published July 11, 2002), machine translation used).

The instant claim is drawn to a method utilizing the inhibitor combinations (DPIV inhibitor and APN inhibitor) for treatment of benign fibrotic and sclerotic diseases, wherein therapy comprises an inhibition of activation, DNA synthesis and proliferation of human fibroblasts.

Ansorge et al teach the combined used of DP IV inhibitor (Lys[Z(NO_2)]thiazolidide) and APN inhibitor (actinonin) for the treatment of atherosclerosis and dermatological diseases (see paragraph 5 of the translated document). Furthermore, the reference teaches simultaneous administration of inhibitors and the administration is as topical application in the fore of creams, ointments, pastes, gels, solutions, spray, liposomes and systemic application to the oral, transdermal, intravenous, subcutaneous, intracutaneous, intramuscular with pharmaceutically acceptable carrier (see paragraphs 6 and 9 of the translated document). Since the elected compound is taught by the reference and is disclosed that the compound can be used to treat dermatological diseases. The reference teaches the treatment of atherosclerosis, which is a species of sclerosis. The reference teaches that

the combination therapy utilizing dermatological illnesses by inhibition of DNA synthesis, meeting the limitation of claims 5, 13, 22 and 24. Therefore, since Ansorge reference teaches the use of DP IV inhibitor (Lys[Z(NO_2)]thiazolidide) and APN inhibitor (actinonin) to treat atherosclerosis and other dermatological diseases, this administration would treat other benign fibrotic and sclerotic diseases. Therefore, the reference meets the limitations of claims 5, 13, 22 and 24.

Response to Applicant's Arguments

11. Applicant argues that "since prevention is no longer recited in the instant claims, it is believed the cited reference does not disclose the presently claimed method."

12. Applicant's arguments have been fully considered but have not been found persuasive. Ansorge reference teaches all of the active methods of the instant claims. Ansorge et al teach the combined used of DP IV inhibitor (Lys[Z(NO_2)]thiazolidide) and APN inhibitor (actinonin) for the treatment of atherosclerosis and dermatological diseases. The reference teaches that the administration of the combination therapy inhibits DNA synthesis. With respect to "wherein the therapy comprises an inhibition of activation, DNA synthesis and proliferation of human fibroblasts" according to MPEP 2111.04: "Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) "adapted to" or "adapted for" clauses;

(B) "wherein" clauses; and

(C) "whereby" clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. In *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a "whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." Id. However, the court noted (quoting Minton v. Nat'l Ass'n of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a "whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited." Id. <". In the instant case, it is not deemed that the "wherein" clause limits the claim to particular structural features.

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). No claim is allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anish Gupta/
Primary Examiner, Art Unit 1654

/J. H./
Examiner, Art Unit 1654